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Is the BCG vaccine a useful tool against COVID-19?

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Abstract The Bacillus Calmette–Guérin (BCG) vaccine has been used since 1921 initially for protection against tuberculosis. BCG acts through stimulation of cell-mediated adaptive immunity with activation of the Th1 cells and production of interferon gamma. Additionally, it is able to stimulate the immune system in a nonspecific manner, which results in effectiveness of the BCG against non-mycobacterial infections and in some malignant, autoimmune, and inflammatory diseases. Recently, its potential use in the fight against the coronavirus disease 2019 (COVID-19) pandemic has been suggested. This is based upon the concept of BCG-induced trained innate immunity—a memory-like response of the innate immune system that can realize greater protection in case of re-infection. This hypothesis represents a milestone in the potential use of the BCG vaccine in the fight with the novel coronavirus.

The Bacillus Calmette–Guérin (BCG) vaccine: history and present

Bacillus Calmette–Guérin (BCG) vaccine was launched in 1921 and is the only vaccine currently in use for protection against tuberculosis (TBC)—the disease that is one of the top 10 causes of death and the leading cause of death from a single infectious agent in the world.[1,2]

The BCG vaccine was created by two French scientists: Albert Calmette (1863-1933) and Camille Guérin (1872-1961) from the Pasteur Institute, Lille, France. After 13 years of trying to subculture the *Mycobacterium bovis* strain on bile-potato medium, they finally succeeded in obtaining a newly less virulent strain, possibly as a result of genetic changes. The strain was first used for immunization of humans in 1921. The *M bovis* BCG (live attenuated strain of *M bovis* by Calmette and Guren) was initially used in its oral form. Subsequently, it became generally accepted that the most accurate method of BCG vaccination is intradermal application, due to the huge number of antigen-presenting cells in dermal zone—dendritic cells and macrophages.[3]

After its development, the original vaccine strain of *M bovis* was transferred to other laboratories, where the same procedure of cultivation has been repeated. Currently, numerous manufacturers around the world produce their own BCG vaccine strain. As a result, the BCG vaccines in current use may not be identical, because there are significant variations of the strains.[4] Recent genomic studies and comparative analyses have concluded that the various strains have evolved and differ from the original 1921 BCG vaccine first used; however, these mutations in the BCG strains have not shown to affect BCG-associated protection and/or adverse effects. Currently, there is no worldwide consensus about which strain of BCG has the best properties for use in the general population.[5,6]

Several popular BCG strains include the following:

- French (Pasteur) strain
- Danish strain
- Glaxo strain
- Tokyo strain
- Moscow strain
- Tice strain

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The names of the strains reflect the country or the laboratory in which they are produced.[7]

The schedule for BCG vaccination for TBC prevention is not the same in different geographic areas and varies according to the local epidemiology of the disease.[8] Generally, the first dose of the BCG vaccine is given in infancy, which is often followed by additional vaccinations throughout childhood. In some countries, the schedule for revaccination is universal, whereas in others the revaccination is performed based on the lack of tuberculin sensitivity or the absence of a typical scar.[8] The official recommendation of the World Health Organization (WHO) is a single dose of BCG in infancy. It includes vaccination of all newborns in countries with a high incidence of TBC and a high risk for potential complications such as meningitis and sepsis.[9]

The use of BCG vaccine for routine immunization has decreased or has been discontinued due to the low rate of TB in many industrialized countries, although selective vaccination of high-risk groups may still be performed. In some countries, such as the Netherlands and the United States, BCG vaccination was never included in their national immunization programs.

Effectiveness of BCG vaccine and mechanism for induction of specific immunity in TB

The BCG vaccine acts through stimulation of the cell-mediated adaptive immune response and activation of Th1 immunity.[10] Such immunization with BCG leads to activation of CD4+ and CD8+ T-cells and increased production of interferon (IFN)-gamma. This cytokine, INF-gamma, plays a key role in the anti-mycobacterial activity of the macrophages and stimulates B-cells to produce antigen-specific antibodies.

Two important aspects of the immunity induced by BCG vaccination in the host are not understood:

1. The duration of the BCG-induced immune response
2. The mechanism for vaccine-induced cell-mediated immunity[11,12]

Similarly, the clinical effectiveness of the BCG vaccine continues to be controversial.[13] Observations on its safety and effectiveness made in the 1940s and 1950s were reviewed in the early 1990s with the conclusion that the BCG vaccine has a good safety profile; however, efficacy against pulmonary tuberculosis could not be shown.[14]

Today, on the basis of large-scale randomized, controlled clinical trials, and case-control studies, it is broadly accepted that the BCG vaccine induces significant specific protection in patients with tubercular neonatal meningitis and in children with disseminated tuberculosis. There is almost no effect in adults and the elderly or in those with latent TB infection.[15] Based on these studies, the effectiveness of BCG is considered to be only partially effective against TB and should be limited for use in children.[16,17] Studies on the effectiveness of the BCG vaccination against meningitis and miliary tuberculosis in neonates are inconsistent.[18]

Hypothetically, these differences in the effectiveness of the BCG vaccine could be due to genetic variations in the vaccine strains, variations in the immunization schedules, genetic variations of the host, or interference of the human immunity with certain parasites.[19-21] The last is explained by the interplay between Th2-immune response against parasites and Th1-response that predominates in TB infection.

Despite the unsolved questions about the effectiveness of the BCG vaccine, this century-old vaccine remains the only registered vaccine against TB and continues to be used worldwide.[22] BCG also has consistent benefits in protection against leprosy.[23-25] *Mycobacterium leprae* is a member of the same genus *Mycobacteria* as *M bovis* and has common antigenic determinants with the BCG vaccine strain.

Nonspecific immune stimulation and effectiveness of BCG against infections, other than TBC, and in malignant, autoimmune, and inflammatory diseases

A well-established hypothesis is that BCG stimulates the immune system in a nonspecific manner; for example, BCG is currently used for the treatment of some types of malignancies, including bladder cancer and multiple myeloma. The induction of the immune response is attributed to nonspecific mechanisms.[26,27] The action of BCG vaccine in some inflammatory and autoimmune diseases[28] may be mediated by the impact of the vaccine on the cytokine production of T-regulatory cells (T-regs) and Th17 lymphocytes.

BCG may have nonspecific beneficial effects in children from both developing and developed countries by reducing morbidity and mortality unrelated to *M tuberculosis*. Several clinical studies from different geographic areas, mostly involving children, suggest a nonspecific protective effect of the BCG vaccine against bacterial and viral infections; for example, BCG vaccination in neonates influences the immune response to standard vaccines given in early life.[29] These results are attributed to the adjuvant effect of BCG vaccine through stimulating the maturation of the dendritic cells.

A case-control study[30] in Guinea-Bissau showed a beneficial effect of BCG vaccination against acute lower respiratory tract infections and respiratory syncytial virus in infants. A randomized clinical trial[31] showed a 17% decline in the mortality of low-birth-weight children from West Africa who were BCG-immunized in the previous year. This report favored the beneficial effect of the BCG vaccine against other infections. Similar results have been reported in a small randomized controlled study in neonates,[32] where there was a lower mortality from infections in the BCG-vaccinated cohort.

The beneficial effect of the BCG immunization on the resistance to non-TBC infections has been confirmed by two randomized clinical trials in Guinea-Bissau, where a 45% reduction of overall mortality has been reported in vaccinated neonates.[33] Similar results are found in Spain with BCG-vaccinated and nonvaccinated children. There was an average of 40% decrease in hospitalization due to respiratory infections, and sepsis not related to tuberculosis was observed in immunized children.[34] Two additional case-control studies found the protective effect of BCG vaccination in children against lower respiratory tract infections and bacteremia-related mortality.[30,35,36]

A global prospective study across 19 countries conducted over a period of 25 years again showed that the BCG immunization is associated with 17% to 37% of reduction of suspected acute lower respiratory infections in children <5 years of age.[37] Several clinical studies have focused on the nonspecific protective effect of the BCG vaccination in adults and the elderly. BCG immunization in patients over 65 years old with comorbidities may decrease the risk of developing pneumonia.[38] A single dose of BCG vaccine monthly for three consecutive months may significantly reduce the risk of acute upper respiratory tract infections in this age group through increasing Th1 and T-reg immune responses.[39]

A randomized, placebo-controlled pilot study on healthy adults has shown that BCG vaccination before an influenza vaccination against the 2009 influenza A pandemic resulted in a more pronounced and accelerated induction of functional antibody responses.[40]

BCG-induced trained innate immunity: a memory-like immune response

In the last decade, the cellular and molecular mechanisms of nonspecific immunity induced from BCG vaccine have been studied in detail. New facts were obtained and were interpreted in the aspect of nonspecific protection against the COVID-19.[41]

The innate immunity represents the first line of defense against infections and realizes nonspecific protection without memory immune responses as it is in the case of adaptive immunity. There are increasing scientific data that innate immune mechanisms can realize greater protection in case of re-infection. This can be interpreted as a memory-like response. Some infections and vaccinations can induce broad protection against other pathogens exactly through innate immune mechanisms.[42,43] Such innate immune responses with a new type of immunologic memory are known as trained innate immunity.[44]

In the case of the BCG vaccine, the induced trained innate immunity may result from an interaction between toll-like receptors and conservative structures from BCG bacteria cell walls. This leads to epigenetic and metabolic reprogramming of the innate immune cells and development of trained innate immunity. Subsequently, the activated macrophages and NK cells stimulate the production of a number of cytokines, which are characteristic for such acute inflammation, due to tumor necrosis factor (TNF) α and interleukin (IL)-6.[45,46]

Several scientific groups have investigated whether BCG can stimulate trained innate immunity in infants. There were enhanced innate responses to nonspecific stimuli following infant BCG vaccination in a cohort both in West Africa[47] and in the United Kingdom.[48] Similar results have been reported following neonatal BCG vaccination.[49]

The induction of trained immunity is at least partially responsible for nonspecific cross-protection.[50] This hypothesis, pending rigorous clinical trials, is the milestone for the potential use of the BCG vaccine in the fight with the novel coronavirus.

BCG vaccine and coronavirus disease (COVID-19)

Vaccination of adults and the elderly with BCG to prevent infection or reduce the number mortality from COVID-19 is a very attractive idea.[41,51] There would be no concern about the safety of BCG vaccine.

Because COVID-19 is a global health emergency, many clinical trials have been initiated to assess the nonspecific boosting effect on immunity induced by the BCG vaccine. Currently, the data for epidemiology of COVID-19 indicate a lower rate of COVID-19-related mortality in the developing countries with a high level of routine BCG immunization in the general population.[52]

Two large studies on the relation of the previous BCG vaccination and risk of death from COVID-19 are intriguing. In the first multinational study, the authors compare BCG vaccination policy and COVID-19 cases and deaths. The results show a strong correlation between BCG vaccination and incidence of COVID-19 cases. The conclusion is that countries with robust BCG vaccination policies have lower case fatality rates of SARS-CoV-2.[53]

The second recent study also suggests an inverse correlation between BCG vaccination and severe coronavirus disease and mortality rates.[54] The authors consider the influence of a number of factors that can affect the nonspecific effectiveness of BCG vaccine and may explain the broad differences between countries.

A significant inverse correlation between the BCG vaccination index and deaths from COVID-19 has been detected—every 10% increase in the BCG index has been associated with a 10.4% reduction in COVID-19 mortality. The high mortality rates in France and the United Kingdom are possibly a result from the BCG immunization of older children in contrast to Germany and Scandinavian countries, where an early BCG vaccination is routinely performed.[54]

BCG immunization of adults and elderly: ongoing randomized clinical trials of the BCG vaccine for COVID-19

A growing number of BCG vaccines presented in a CEBM (Centre for Evidence-Based Medicine) review are currently being investigated in various studies worldwide.[55] The idea in all those trials is to use the BCG vaccine as a potential preventive measure against SARS-CoV-2 for adults and the elderly, who are known to have an increased risk of a severe clinical course of COVID-19 and death. Catch Health Technology Review has reported information about 16 controlled randomized clinical trials (phase II, 1 trial; phase III, 3 trials; phase IV, 12 trials) up to June 23, 2020. All trials have selection criteria and use selected methods of investigation.[56]

Most of the trials have included BCG-immunized subjects who have been at a high risk for infection with the new virus—healthy adult health care workers (HCWs) (medical or nonmedical) from COVID-19 hospitals who are directly being exposed to the virus. There are different BCG strains used:

- Germany and France—a strain recombinant vaccine VPM 1002
- Greece—Moscow strain
- India—Danish strain
- USA—Tice strain
- Netherlands—BCG strain
- Australia and Europe—Danish strain
- South Africa—Danish strain
- Colombia—BCG strain
- Canada—recombinant vaccine VPM 1002

Participants receive a single dose of BCG vaccine intradermally (or placebo) and are followed for 6 to 12 months.

All study participants in the French clinical trial were vaccinated in childhood, because BCG vaccination was mandatory in France for neonates until 2007 and in HCWs until recently. The French study provides a unique situation to evaluate the effect of revaccination with BCG in the context of BCG priming decades before the revaccination.[55]

Interesting results are also expected in the case of trials that use recombinant candidate BCG vaccine VPM 1002. VPM 1002 is based on the traditional BCG vaccine, which was developed at the beginning of the 20th century and is indicated to prevent tuberculosis recurrence.[57] A new study has been recently undertaken in India to investigate the effectiveness of BCG in preventing morbidity and mortality due to COVID-19 in subjects 60 to 95 years of age.[58] The regimen is the same as applied to newborn babies as a part of the national immunization program.

Discussion

The hypothesis that BCG vaccination might be a potent preventive measure against SARS-CoV-2 infection and/or may reduce disease severity in high-risk groups is intriguing. It is reasonable to predict a beneficial effect of this vaccine on the basis of the knowledge from epidemiologic studies about the nonspecific cross-protection induced from the BCG vaccine, and from the new information about trained immunity.[41,51]

There are two important questions arising from current studies:

1. Can the BCG realize basic or at least transient protection against COVID-19 in adults and elderly people? If yes, it will be very useful for high-risk groups—HCWs and patients with comorbidities, such as obesity, diabetes, or cardiovascular diseases. How adults will react to the BCG immunization is not clear. Results from the large number of ongoing prospective randomized clinical trials are awaited.[56-58]
2. How long does early neonatal BCG immunization provide protective immunity? Many countries in Eastern Europe and some in Asia have active universal BCG immunization programs, and it is possible to compare the protection against COVID-19 in older age with the protection in countries where a routine BCG infant immunization is not applied, such as most of Western Europe and the United States.

Currently, it is well established that BCG vaccine possesses immune-boosting properties, which justify its use in the treatment of several malignancies.[26,27] A large number of studies confirm its ability to ensure nonspecific protection in children against bacterial and viral respiratory infections.[30,31] Novel data show that BCG vaccine can stimulate nonspecific immune memory in the context of innate immunity.[48-50] There is a tendency toward both lower morbidity and mortality from COVID-19 in countries with universal BCG vaccination in childhood.[53,54]

Conclusions

The statement of WHO is that currently there is no sufficient evidence that BCG vaccine can protect people from COVID-19 infection. It is not recommended for prevention of COVID-19 until data from ongoing clinical trials are reported.[9] The Global Alliance for Vaccines and Immunizations has given a similar statement.[14]

Despite the optimism for development of a specific vaccine against SARS-CoV-2, it seems currently unrealistic that it would be globally and rapidly introduced for massive prophylaxis of COVID-19. The only alternative to a specific vaccine is a nonspecific stimulation of immunity that will increase the chances for resistance to the novel coronavirus and

thus decrease related morbidity and mortality. BCG vaccine could provide basic or even partial protection against SARS-CoV-2. Such ongoing clinical trials with the BCG immunization of risk groups could provide the immune-boosting potential of the BCG vaccine and justify its application for COVID-19 protection.

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